Reviewer's report

Title: The cost-effectiveness of exercise referral schemes

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Reviewer: Marieke F. van Wier

Reviewer's report:

The manuscript describes the cost-effectiveness of exercise referral schemes (ERS) in the United Kingdom (UK), from the NHS perspective with a lifetime horizon. The strategy of interest is referral of primary care patients aged 40 to 60 not meeting current guidelines for sufficient physical activity (PA) to a third party. The third party then prescribes and monitors an exercise program tailored to individual patient. The comparator was usual care, which was not further described. Cost-effectiveness was established using a modelling approach. The model consisted of a decision tree, based on a previous model developed by NICE. Probabilities for moving from an inactive to an active state were derived from an, as yet, unpublished systematic review. Probabilities for developing three PA-related outcomes, i.e. coronary heart disease (CHD), stroke and type 2 diabetes (T2DM), were derived from literature and from the Health Survey for England. Mean cost of ERS was based on a single study and judged representative by an expert group. Treatment costs associated with CHD, stroke and T2DM care came from published cost estimates. Assumptions were made on age of onset and life-expectancy. These were combined with annual treatment costs to estimate lifetime treatment costs. Estimates of associated lifetime QALYs were derived from health state values for each condition, in combination with life-expectancy after onset of the condition. The main analysis concerned the general inactive population. Subgroup analyses were performed for individuals diagnosed with obesity, hypertension and depression. Sensitivity analyses were done for the main analysis. To address the uncertainty around the model inputs, probabilistic sensitivity analysis with 10,000 Monte Carlo simulations was performed. Also, deterministic sensitivity analyses were done.

The results showed that ERS are associated with a modest increase in lifetime costs and QALYs gained. They have an 88% probability of cost-effectiveness at a ceiling ratio of £30,000/QALY. ICERs tended to be lower in the subgroups with pre-existing illness. However, cost-effectiveness of ERS is highly sensitive to small changes in the assumptions regarding effects and costs. As there is still considerable uncertainty about effectiveness of ERS, uncertainty about their cost-effectiveness remains.

The study presents a partial update of a study that was performed in 2006 and will, as I believe, be used to update NICE guidance with regard to exercise referral schemes. The analysis performed looks solid, and appropriate use was made of sensitivity analyses. The authors also present a balanced discussion of their results and draw a conservative conclusion. However, I have a number of
remarks regarding parts of the manuscript that need clarification. Furthermore, the major input for the decision model, the effectiveness of ERS, is based on an as yet unpublished systematic review. I recommend that publication be postponed until this review has been peer reviewed and accepted for publication.

Major compulsory revisions:

1. Methods-Modelling approach-risks of developing health states associated with inactivity: I find the explanation of how probabilities were estimated utterly confusing. As it says here, probabilities for developing the conditions among sedentary individuals in the non-ERS cohort (only in the non-ERS cohort?) were generated from the prevalence of the conditions in the sedentary population identified in the HSE 2006 dataset. Probabilities for developing the conditions in active individuals were derived from RR estimated identified in three publications. Subsequent adjustment (?) of the control (?) probability was done for each condition in the ERS cohort. How was adjustment done? And of what?

2. With regard to probabilities for developing health states, please explain if these are general population risks or risks particular to the age group 40-60.

3. Table 2 should list the uncertainties around the point estimates.

4. Besides the distribution used for each parameter in the PSA, alpha and beta used for each parameter should be mentioned.

5. Please explain why the CE-plane is expressed in multiplications (100 times) of cost and outcome, or change to original values.

Minor essential revisions:

1. Introduction, paragraph 1. “In spite of this, only…”. ‘This’ refers to the high societal costs of physical inactivity in the previous sentence, whereas the author probably means to refer to the health effects. I suggest rephrasing the sentence.

2. Methods-Modelling approach-Effectiveness of ERS/comparator, paragraph 2: reference 16 states that “All healthy adults aged 18–65 years should aim to take part in at least 150 min of moderate intensity aerobic activity each week, or at least 75 min of vigorous-intensity aerobic activity per week, or equivalent combinations of moderate- and vigorous-intensity activities” and not a minimum of 90-150 minutes/week. Please rectify.

3. Methods-modelling approach-Effectiveness of ERS/comparator, paragraph 2: explain what is meant with dose-response relationship. Dose, as in number of PA minutes per week, or dose as in number of years being physically active? The term is confusing within this context as it usually refers to the former.

4. Methods-Modelling approach-risks of developing health states associated with inactivity: give a reference for the systematic review mentioned in sentence 1.

5. Should the model inputs be mentioned among the results?

6. Discussion, paragraph 4: I find it unclear how the assumption that having sufficient PA after ERS is lasting relates to the earlier part of the paragraph.

7. Typos/grammatical errors:
- Methods-modelling approach-Effectiveness of ERS/comparator, paragraph 1, first sentence: compare, add a d, and replace ‘and’ with a comma.
- Methods-Modelling approach-Effectiveness of ERS/comparator, paragraph 2, sentence 2: Add ‘to’ before participation.
- Table 2: Sharper should be Shaper.
- methods-modelling approach-primary outcome measure: life expectancy or life-expectancy?
- there are more errors throughout the manuscript.
- There is no figure 4, nor are there tables 7 and 8.
- 9. Table 1: why the asterisk, because there is no footnote for it. Whereas in table 2 a footnote exists without a corresponding asterisk in the table.

Discretionary revisions:
1. Please consider replacing ‘sedentary’ with (physically) ‘inactive’ as these are increasingly considered to be separate concepts. Physically active people, i.e. meeting PA guidelines, can at the same time be sedentary, i.e. sitting too much, and vice versa. Sedentary behaviour is emerging as an independent risk factor for T2DM and other diseases.
2. Methods-modelling approach-perspective and time horizon, paragraph 1. I think it is more appropriate to refer to the NICE “Guide to the methods technology appraisal” than to a specific guideline as is done with reference 2.
3. I am not a native English speaker, so I am not sure if my remarks with regard to use of language are correct. However, I found the things listed below unusual:
   - introduction, paragraph 3: firstly instead of first.
   - in several places in the manuscript no article is given before a noun. E.g. introduction, paragraph 4: ‘primary care setting’, or in the last sentence ‘UK’.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.